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Scientists show how gene variant linked to ADHD could operate

NIH study in mice shows a potential new target for the treatment of ADHD

A study using mice provides insight into how a specific receptor subtype in the brain could play a role in increasing a person's risk for attention-deficit hyperactivity disorder (ADHD). The research, conducted by the [Intramural Research Program](#) (IRP) at the [National Institute on Drug Abuse](#) (NIDA), part of the [National Institutes of Health](#), could also help explain how stimulants work to treat symptoms of ADHD.

Dysfunction of the dopamine D4 receptor subtype is linked to ADHD as well as other disorders characterized by decreased impulse control, including drug abuse. One subtype variant, D4.7, has been of particular interest because of its increased prevalence in those diagnosed with ADHD. However, the function of this particular variant in ADHD has been poorly understood.

In the study, published in today's *Molecular Psychiatry*, researchers inserted three variants of the dopamine D4 receptor into cells and into mice so that they could investigate differences in biological activities. The researchers found that the D4.7 variant, unlike its D4.2 and D4.4 counterparts, was not able to interact with the short version of the dopamine type 2 (D2S) receptor to reduce glutamate release in a brain region associated with impulsivity and symptoms of ADHD in humans.

"Although previous studies have shown that dysfunctional dopamine D4 receptors are implicated in ADHD, this is the first study to show how this genetic difference might translate into functional deficits seen with this disorder," said NIDA Director Dr. Nora D. Volkow. "Further research is needed to explore how this deficient interaction between receptors might be remedied, which could then lead to new medications for the treatment of ADHD."

Children with ADHD have trouble paying attention and controlling impulsive behaviors, and may be overly active, often resulting in poor school performance and social difficulties. They are also at increased risk for substance use disorders, particularly if their symptoms go untreated.

ADHD is the most commonly diagnosed neurobehavioral disorder of childhood, and the number of children diagnosed continues to rise. According to the Center for Disease Control's [National Survey of Children's Health](#), the number of children aged 4-17 years that were identified by their parent as ever being diagnosed with ADHD increased by 21.8 percent from 2003-2007. By 2007, nearly one in 10 children aged 4-17 years were, at some point, diagnosed with ADHD. Among children with current ADHD diagnoses, 66.3 percent were taking medication for the disorder.

The most commonly used treatment for ADHD involves administering psychostimulant medications. Although these medications alleviate some of the symptoms of ADHD, it is unclear how these compounds act within the brain to do so.

“Our results suggest that psychostimulants might reduce glutamate release by amplifying this D4/D2S interaction,” said Dr. Sergi Ferre, primary author for the study. “These results might also explain why these medications are less efficient in patients with the D4.7 variant.”

For more information on the use of stimulants to treat ADHD, go to www.drugabuse.gov/infofacts/ADHD.html. To learn more about ADHD symptoms, causes, and treatments, with information on getting help and coping, visit www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/complete-index.shtml.

The study, which was the result of a multinational collaboration between researchers at the NIDA IRP, institutes in Spain (the University of Barcelona, the Autonomous University of Barcelona and the University of Navarra), Mexico (the National Polytechnic Institute), and Argentina (the National Council of Scientific and Technical Research), can be found online at: www.nature.com/mp/index.html.

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